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Citation for published version:

Russ, T, Killin, L, Hannah, J, Batty, GD, Deary, I & Starr, J 2019, 'Aluminium and fluoride in drinking water in relation to later dementia risk', *The British Journal of Psychiatry*. <https://doi.org/10.1192/bjp.2018.287>

Digital Object Identifier (DOI):

[10.1192/bjp.2018.287](https://doi.org/10.1192/bjp.2018.287)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

The British Journal of Psychiatry

Publisher Rights Statement:

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Aluminium and fluoride in drinking water in relation to later dementia risk: the Scottish Mental Survey 1932 cohort

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WORD COUNT: 3140

ABSTRACT WORD COUNT: 250

FUNDING: This work was supported by Alzheimer Scotland through the Marjorie MacBeath bequest which funded TCR's salary for one year from 2015-16.

ACKNOWLEDGEMENTS: We are grateful to David Grzybowski at the Drinking Water Quality Regulator for Scotland for providing the water data. Syntax to produce the maps in R was adapted from that posted on Timo Grossenbacher's website (<https://timogrossenbacher.ch/>).

AUTHOR CONTRIBUTIONS: TCR conceived the analysis; LOJK collected the environmental data; TCR and JH collected the health data; IJD was PI of the project which digitised the Scottish Mental Survey 1932 ledgers; GDB and JMS supervised the process of obtaining and cleaning the linked data and previous publications from this dataset; TCR analysed the data and drafted the manuscript; All authors revised the manuscript for critical content.

1 **ABSTRACT**

2 **Background:** Dementia is an important condition but its environmental risk factors are poorly
3 understood. Aluminium and fluorine in drinking water have both been linked with dementia but
4 uncertainties remain about this relationship.

5 **Aims:** In the largest longitudinal study in this context we set out to: (1) explore the individual effect of
6 aluminium and fluoride in drinking water on dementia risk; and (2) with fluorine having the capacity to
7 increase absorption of aluminium, we also examine any synergistic influence on dementia.

8 **Methods:** We used Cox models to investigate the association between mean aluminium and fluoride
9 levels in drinking water at their residential location (collected 2005-2012 by the Drinking Water Quality
10 Regulator for Scotland) with dementia in members of the Scottish Mental Survey 1932 cohort who
11 were alive in 2005.

12 **Results:** A total of 1972/6990 individuals developed dementia by the linkage date in 2012. Dementia
13 risk was raised with increasing mean aluminium levels in women (HR per SD increase 1.09, 95%CI
14 1.03-1.15; $P<0.001$) and men (1.12, 1.03-1.21, $P=0.004$). A dose-response pattern of association was
15 observed between mean fluoride levels and dementia in women (1.34, 1.28-1.41, $P<0.001$) and in men
16 (1.30, 1.22-1.39, $P<0.001$) with dementia risk more than doubled in the highest quartile compared to
17 the lowest. There was no statistical interaction between aluminium and fluoride levels in relation with
18 dementia.

19 **Conclusions:** Higher levels of aluminium and fluoride were related to dementia risk in a population of
20 men and women who consumed relatively low drinking water levels of both.

21 **Declaration of interest:** none.

22 INTRODUCTION

23 Dementia is a major, growing public health problem and, with disappointing results from treatment-
24 orientated studies, identifying risk factors for primary prevention is key.(1) Whereas genetic risk and
25 lifestyle factors are important in the development of dementia, there is evidence that environmental
26 factors may also play a role.(2-5) One potentially important environmental risk factor is drinking water
27 quality. Aluminium can occur naturally in water but is also widely used in water treatment, including in
28 Scotland.(6, 7) Aluminium has a wide variety of neurotoxic effects and there is some evidence
29 supporting aluminium influencing β -amyloid oligomerization;(8) it has not been linked with other
30 health outcomes.(7) In terms of epidemiological evidence, only one longitudinal study has investigated
31 aluminium in drinking water and dementia,(9) though a number of cross-sectional studies – many small
32 in size – make up a complex literature:(4) seven studies found a positive association between aluminium
33 levels in drinking water and dementia and five found no association or conflicting findings.
34 Furthermore, fluorine can increase aluminium absorption from drinking water since aluminium fluoride
35 has greater bioavailability.(10) Fluoride occurs naturally in water and is not added in Scotland.(6) High
36 levels of fluoride affects skeletal tissues and possible links with cancer have been identified but low
37 levels of intake protect against dental caries.(7) Accordingly, the present study aims to explore the
38 association between aluminium and fluoride levels in drinking water with dementia in a large
39 longitudinal study in Scotland where such levels are below levels considered acceptable according to
40 guidelines (mean aluminium level in Scotland 37.4 μ g/L compared to regulatory limits in Scotland
41 <200 μ g/L; mean fluoride [F⁻] level in Scotland 53.4 μ g/L compared to WHO fluorine [F] guideline
42 value <1500 μ g/L). This is the largest longitudinal study on the topic to date and the first to explore
43 aluminium and fluoride together.

44

45 METHODS

46 Study sample

47 This study used data from the Scottish Mental Survey 1932 (SMS1932); in this almost all people born in
48 1921 and at School in Scotland in June 1932 took part in a comprehensive national intelligence test at
49 mean age 11 years as previously described in detail(11) 5.6% of participants did not take part in the test
50 because they were absent from school but were still recorded in the test ledgers without a test score.
51 The intelligence test was the Moray House Test no. 12 from which an IQ score was derived, corrected
52 for age in days at the time of testing. Participants have been passively followed up into later life using
53 anonymised probabilistic record linkage to hospital admissions and death certificate data, as described
54 in detail in a previous report.(2) Approximately 43% of the 86,250 test participants (apart from those
55 living in the counties of Angus, Fife, and Wigtown; SMS1932 ledgers for these locations have been lost)
56 were identified in later life. Dementia cases were identified by any mention of codes 290.0 to 290.4,
57 290.8, 290.9, 291.1, 291.2, 294.1, 294.2, 294.8, 294.9, and 331.0 to 331.9 for ICD-9 and codes F00-
58 F05.1, F09, G30, and G31 for ICD-10 recorded on electronic medical records or death certificates after
59 2004. A subsample was also identified from primary care records, specifically the Greater Glasgow &
60 Clyde Nursing Homes Medical Practice which exclusively treated residents of nursing homes. An
61 individual's residential location (postcode sector) was recorded from the record which first mentioned
62 dementia for those who developed this condition. For those who did not develop dementia, their
63 residential location at the first record after the age of 60 years (the earliest possible due to the electronic
64 medical records) which may have been at death. We excluded individuals who died before the exposure
65 period which began in 2005. This study received ethical approval from the Scotland A Research Ethics
66 Committee (10/S1103/6). Collecting individual informed consent from participants was not feasible.

67

68 **Environmental data**

69 Water quality data were obtained from the Drinking Water Quality Regulator for Scotland (DWQR) for
70 the years 2005 to 2014. The DWQR is responsible for regulating public water supplied by Scottish
71 Water. Prior to the establishment of Scottish Water in 2002, the responsibility for monitoring water
72 quality was the responsibility of separate local authorities. Aluminium and fluoride levels in drinking
73 water (micrograms per litre) were extracted from the database.

Sampling sites were identified by longitude and latitude and were widely distributed across Scotland, particularly where the population is more concentrated (**Supplementary Figure 1**). Of 50,378 aluminium and 15,808 fluoride sampling sites, the location of the site was missing for 1128 and 556 locations, respectively. These sites were assigned the location from the closest row above in the database. **Supplementary Table 1** shows the number of sampling sites for aluminium and fluoride in each year (2005-2012) and summarises the levels of these substances in drinking water in Scotland.

We used the `idw()` function from the `gstat` package for R for Windows version 3.4.3 to interpolate values for aluminium and fluoride using Inverse Distance Weighting across a spatial grid with spacing of 0.1 degrees of longitude or latitude for each year separately. This allowed us to estimate values for areas where no measurements had been made. The mean values for each grid area within every postcode sector in Scotland were then calculated (again for each year separately) which were assigned to each individual based on their residential location. We used each individual's age to create dummy variables indicating whether they were alive for any of each of the years from 2005 to 2012. These dummy variables were then used to calculate a 'personal' mean value for aluminium and fluoride using only data from the years in which the individual was alive to be exposed. For example, an individual who died at the age of 88 would have been alive in the years 2005 to 2009 inclusive; data from 2010-2012 would be ignored for this person. These 'personal' mean values were standardised and centred on zero such that a unit increase indicated one standard deviation increase in the original scale (10.0µg/L for aluminium and 16.0mg/L for fluoride). We also calculated quartiles of aluminium and fluoride values to allow us to examine the shape of any association identified.

Socioeconomic data

In order to account for socioeconomic position, we obtained Scottish Index of Multiple Deprivation (SIMD) which provides a relative measure of deprivation by small area (datazone, of which there are 6505 in Scotland in the 2012 data we used) and incorporates the following domains: employment; income; health; education, skills and training; geographic access to services; crime; and housing.(12)

100 Each individual was assigned a rank based on the datazone in which they lived, either at the time
101 dementia was first mentioned or the first record after the age of 60 years.

102

103 **Statistical modelling**

104 After confirming that the proportional hazards assumption was valid using the `cox.zph()` function from
105 the survival package in R (all $P > 0.1$), we constructed Cox proportional hazards models for the
106 association between aluminium and fluoride levels in drinking water with dementia in men and women
107 separately. Age in years over the age of 84 was the timescale and all models were additionally adjusted
108 for age-11 IQ since this has also been linked with dementia risk in this cohort.⁽¹³⁾ We made the
109 decision to analyse separately by gender – despite preliminary analyses suggesting there was no
110 statistical interaction by sex ($P > 0.5$) – because of evidence that the pattern of geographical variation in
111 dementia risk varies between men and women (**Supplementary Figure 2**).⁽²⁾ We conducted a
112 sensitivity analysis, additionally adjusting the above models for SIMD rank. We additionally constructed
113 a joint model investigating for a statistical interaction between aluminium and fluoride. Maps were
114 produced in R using the `ggplot2` package.

115

116 **RESULTS**

117 The sample comprised 19,272 men and 18,325 women, but 4408 men and 3446 women were missing
118 residential location in later life. Men were overrepresented in those missing residential location
119 ($\chi^2=93.8$, $P < 0.001$) but, while statistically significant due to the large sample size, individuals with
120 missing residential location scored only 0.9 IQ points lower than those who had location data
121 ($P < 0.001$). Given the known effect size of IQ in relation to dementia, a difference of 0.06 standard
122 deviations is unlikely to be important.⁽¹³⁾ A further 9536 men and 7984 women died before the
123 monitoring period began in 2005, and 2600 men and 2633 women were missing childhood IQ. This
124 resulted in an analytic sample of 2728 men and 4262 women alive in 2005 of whom 622 men and 1350
125 women were identified as having subsequently developed dementia. All participants were approximately

126 84 years old at the start of the exposure period and were followed up for a mean of 2.7 (SD 2.1, range
127 0-7) years.

128 Levels of aluminium and fluoride in drinking water derived from DWQR data are shown in
129 **Supplementary Table 1** and **Figure 1**. Mean aluminium levels in drinking water in participants were
130 37.4µg/L (SD 10.0, range 10.5-92.8) and mean fluoride levels were 53.4µg/L (SD 16.0, range 23.8-
131 181.1).

132 **Table 1** and **Figure 2** show the results of the Cox proportional hazards models. Higher mean
133 aluminium levels in drinking water were associated with an increased risk of dementia in women
134 (adjusted HR per SD increase, 95% CI 1.09, 1.03, 1.15, P<0.001) and men (1.12, 1.03, 1.21, P=0.004).
135 Dementia risk was increased in all quartiles compared to the lowest but **Figure 2** suggests no dose-
136 response pattern of association. Higher mean fluoride levels in drinking water were associated with an
137 increased risk of dementia in women (1.34, 1.28, 1.41, P<0.001) and men (1.30, 1.22, 1.39, P<0.001) in
138 a stepwise pattern. Dementia risk was more than doubled in this highest fluoride quartile compared to
139 the lowest. Similar to our previous report linking early life cognition with dementia, the aluminium-
140 adjusted HR of dementia per one SD decrease in age 11 IQ was 1.10 (95% CI 1.04, 1.16) in women and
141 1.00 (0.92, 1.08) in men.(14) Living in the most deprived 15% of areas (in late-middle-age or later life)
142 was not associated with an increased risk of dementia compared to the least deprived 85% in women
143 (aluminium-adjusted HR 0.99, 0.86, 1.14; P=0.89) or men (0.93, 0.75, 1.16; 0.53). Adjusting for SIMD
144 rank in addition to age 11 IQ did not alter our conclusions (**Supplementary Table 2**). There was no
145 statistical interaction between aluminium and fluoride levels when both were included in a model
146 together.

147

148 **DISCUSSION**

149 We observed an association between the mean levels of aluminium and fluoride in drinking water and
150 risk of dementia in women and men but found no evidence for an interaction between the two. The
151 pattern of association was different with evidence of a dose-response association for fluoride in women

152 and men but a flatter association of raised risk in all quartiles compared to the lowest quartile of
153 aluminium concentrations. Further adjusting for area-level deprivation did not affect our results.

154

155 **Comparison with other literature**

156 The link between aluminium and dementia has a long and controversial history. The WHO has stated
157 that “[o]n the whole, the positive relationship between aluminium in drinking-water and AD, which
158 was demonstrated in several epidemiological studies, cannot be totally dismissed.”(7) This report
159 highlighted confounding and aluminium intake from other sources (aluminium from drinking water is
160 only about 5% of total intake) as being important factors not frequently dealt with in the literature. We
161 recently reviewed the literature on environmental risk factors for dementia, including aluminium in a
162 variety of forms.(4) This review identified one cohort study and 12 cross-sectional analyses
163 investigating the relationship between aluminium in drinking water and dementia. The only study
164 assigned a high quality rating (1925 participants) found that consumption of aluminium in drinking
165 water in excess of 0.1 mg per day doubled an individual’s risk of dementia (N=461) and tripled their
166 risk of Alzheimer’s dementia (N=364).(9) With 6990 participants, of whom 1972 developed dementia,
167 our study is substantially larger. The remaining studies – all cross-sectional – showed varying results
168 (seven positive, five no effect) but a trend was noted larger studies more likely to observe a positive
169 association between aluminium levels and dementia risk. The four studies identified in the review which
170 examined occupational exposure to aluminium were generally small and gave mixed results. Accidental
171 contamination of drinking water with aluminium sulphate caused cerebral dysfunction which adds
172 weight to the possibility that lower levels of aluminium may carry a health risk.(15)

173 Only one study was identified which investigated the association between fluoride and dementia.(16)
174 This cross-sectional US study linked annual county-level incidence of dementia (calculated from 160
175 hospital case records) to fluoride concentrations in public water supplies. In contrast to the direction of
176 our findings, the county with the highest levels of fluoride in drinking water (4.18mg/L) had the lowest
177 annual incidence of dementia.

178 The levels of both aluminium and fluoride measured in Scotland are relatively low in comparison to
179 the guidelines set by the WHO. Therefore, the fact that we nevertheless observed a dose-response
180 association between aluminium and fluoride levels in drinking water and dementia risk which was not
181 explained by childhood IQ or area-level deprivation is particularly interesting. This suggests that there
182 may be no safe levels of these substances when it comes to dementia risk.

183 The mechanisms of aluminium-related neurotoxicity are multiple and complex but oxidative stress
184 has been highlighted as being of particular importance.(17)

185

186 **Limitations and strengths of the present study**

187 There are a number of limitations to the present study which must be borne in mind, several of which
188 have been discussed previously.(2, 13) First, the linkage to electronic medical and mortality records was
189 incomplete because of emigration, death before the start of the electronic records, and the probabilistic
190 methodology used – less than half of the original 87,498 participants in the SMS1932 were identified in
191 later life (43%). However, this compares favourably with the response in similar studies, for example
192 56% in CFAS-II.(18) Comparing IQ scores – the only baseline data available – in those who were
193 traced and those who were not revealed only trivial differences.

194 Second, the dementia outcome is open to criticism. It was not feasible to follow up thousands of
195 participants across the whole of Scotland and so ‘passive’ anonymised follow up using record linkage
196 was used. However, this relies on the accuracy and completeness of the records used and we have
197 examined this in these Scottish data. The mortality data alone miss approximately 28% of people with a
198 robust diagnosis of dementia from a tertiary-referral memory clinic(19) and the hospital admission data
199 miss about 46% of people with a robust dementia diagnosis agreed by consensus.(20) In the former
200 study, there were also no differences in area-level deprivation or premorbid IQ (estimated by the
201 National Adult Reading Test) at baseline between people who had dementia correctly recorded and
202 those who did not (unpublished results available from the author on request) suggesting that there was
203 no bias in reporting related to socioeconomic position or intelligence. Combining multiple sources, as
204 in the present study, will reduce the chance of missing individuals.(2) Furthermore, when examining

205 associations between putative risk factors and outcomes, missing some cases should not alter an
206 observed association and, indeed, this is the approach to follow up being taken by the N=500,000 UK
207 Biobank study.(21) However, this methodology does not easily allow disaggregation of dementia into
208 the individual diseases which cause this syndrome – Alzheimer’s dementia, vascular dementia, dementia
209 with Lewy bodies, etc. – since so many records use generic dementia codes rather than disease-specific
210 ones.

211 Third, water data were only available for the period 2005-2012. Thus, the sample who had survived
212 to the start of the exposure period was substantially reduced from baseline. The sample sites were
213 distributed widely across Scotland (**Supplementary Figure 1**) and the number of sites was
214 approximately constant each year (**Supplementary Table 1**). The spatial interpolation used to estimate
215 values for areas where no measurement occurred introduces uncertainty but, in fact, few participants
216 would live far from a sampling site since samples were co-terminous with areas of population density.
217 Related to this exposure period is that we know nothing of the participants’ exposure to drinking water
218 prior to 2005, i.e. for the first 84 years of their lives. It seems reasonable to assume a low level of
219 exposure to aluminium and fluoride during this period, but we cannot provide further justification for
220 this assumption. Given that neurodegeneration starts decades before the clinical onset of dementia
221 symptoms, it may be exposure many years before dementia diagnosis that is important, but we have no
222 information about this.

223 Fourth, levels of aluminium and fluoride in drinking water vary substantially over the exposure
224 period (**Supplementary Table 1, Supplementary Figure 3**). Aluminium levels show a general decline
225 over the whole period. Indeed, this fact, combined with our findings, might suggest that a decline in
226 levels of aluminium in drinking water could be a further partial explanation for the decrease in
227 dementia rates observed in Europe and North America.(22) Fluoride levels are higher at the start and
228 end of the exposure period; the mean value represents a cumulative exposure but the variability of
229 measurements over time highlights a limitation of the present analyses. Within postcode sectors, there
230 was similar variation. The within-area correlation between 2005 and 2012 values is $r=0.49$ ($P<0.001$)
231 for aluminium and $r=0.012$ ($P<0.001$) for fluoride. In addition, participants were only located at one

232 point in time and it was assumed that they did not move during the study period, which may not be
233 valid. However, our study was longitudinal in design which is more robust than a cross-sectional study,
234 particularly when considering Bradford Hill's temporality criterion when considering whether the
235 observed association might be causal.

236 Finally, a criticism of much of the literature in this area is a lack of consideration of confounding.
237 There were very few data recorded at baseline in the SMS1932. We adjusted for childhood IQ since this
238 has previously been linked with dementia.(13, 23-25) Furthermore, higher fluoride concentrations in
239 water have been linked with lower childhood intelligence in multiple studies.(26) We were additionally
240 able to adjust models for SIMD to take into account relative deprivation, albeit at an area-level. On the
241 other hand, the fact that this is a narrow age cohort – all born in 1921 – means that the sample will be
242 more homogenous than a broader aged sample. For example, there will be no cohort effects
243 complicating our findings.

244

245 **Implications**

246 Aluminium is widely used in water treatment to reduce organic matter and to improve other water
247 parameters and is also influenced by water acidity.(7) Low fluoride levels in drinking water are
248 beneficial for teeth but high levels are harmful.(7) Thus, both these substances are widely present in
249 drinking water, albeit at levels considered acceptable. However, our findings suggest that even these
250 relatively low levels of aluminium and fluoride are associated with deleterious effects on dementia risk
251 which should be weighed against their beneficial uses. We must be circumspect in the conclusions we
252 draw from the present study, not least because only limited account could be taken of potential
253 confounders. However, this is clearly an area which deserves further investigation, given the substantial
254 and growing global public health impact of dementia.

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TABLE 1. Adjusted hazard ratios and accompanying 95% confidence intervals for the association between mean aluminium and fluoride levels in drinking water and dementia in men and women: the Scottish Mental Survey 1932 cohort

	N ^a	Dementia N	Hazard ratio ^b (95% confidence interval)				HR ^b (95% CI) per SD increase	P _{trend}
			Q1 (low)	Q2	Q3	Q4 (high)		
Aluminium								
Women	4262	1350	1 (ref.)	1.37 (1.17, 1.60)	1.30 (1.11, 1.51)	1.41 (1.20, 1.64)	1.09 (1.03, 1.15)	<0.001
Men	2728	622	1 (ref.)	1.28 (1.01, 1.61)	1.25 (0.99, 1.57)	1.48 (1.18, 1.85)	1.12 (1.03, 1.21)	0.004
Fluoride								
Women	4262	1350	1 (ref.)	0.92 (0.79, 1.07)	1.15 (0.99, 1.34)	2.32 (2.01, 2.68)	1.34 (1.28, 1.41)	<0.001
Men	2728	622	1 (ref.)	1.05 (0.84, 1.32)	1.49 (1.19, 1.86)	2.65 (2.14, 3.29)	1.30 (1.22, 1.39)	<0.001

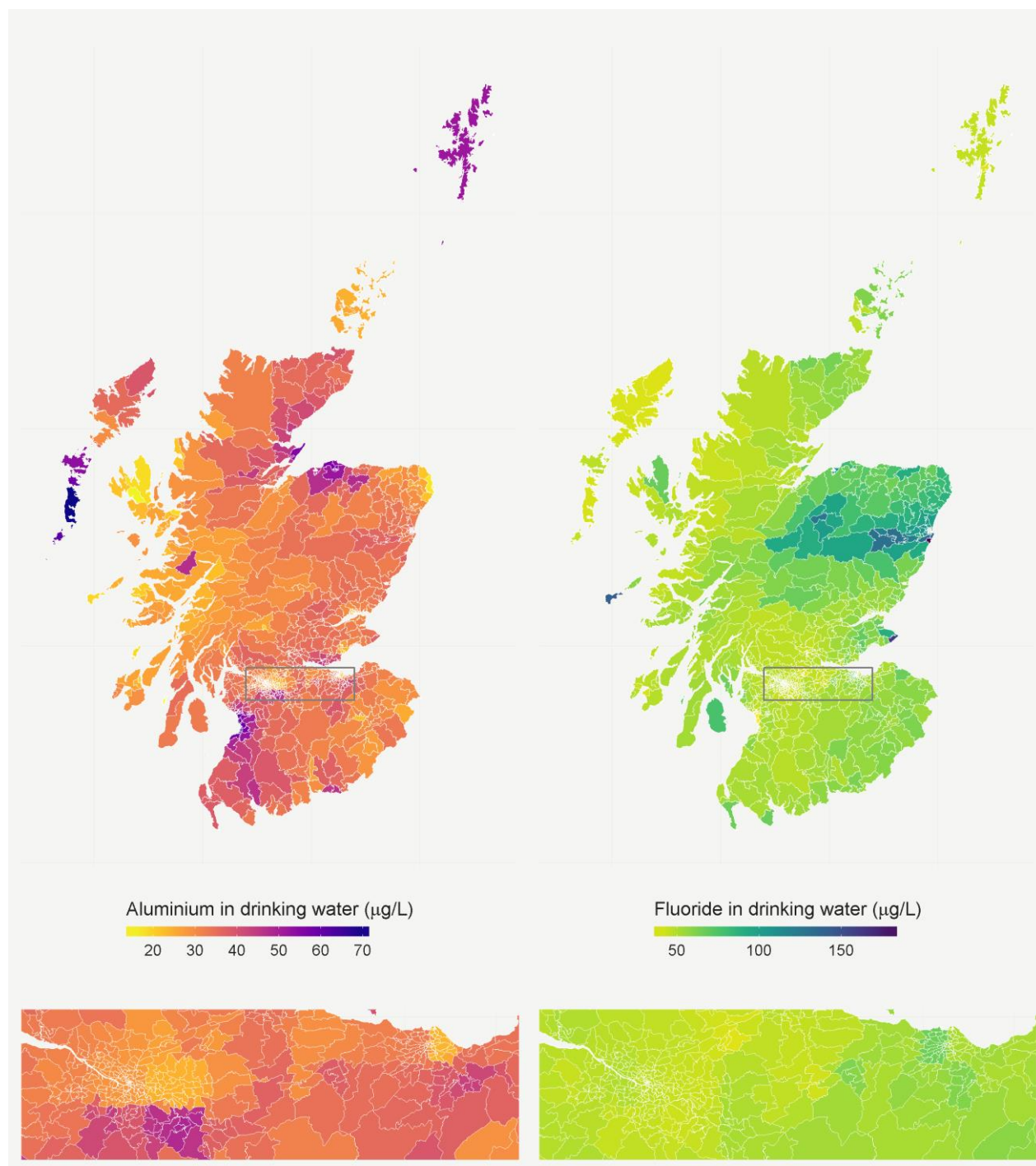
^a SMS1932 participants who survived to 2005 (the start of the exposure period)

^b Hazard ratio adjusted for age 11 mental ability

Cut points for aluminium quartiles were 30.8, 35.5, and 41.1µg/L

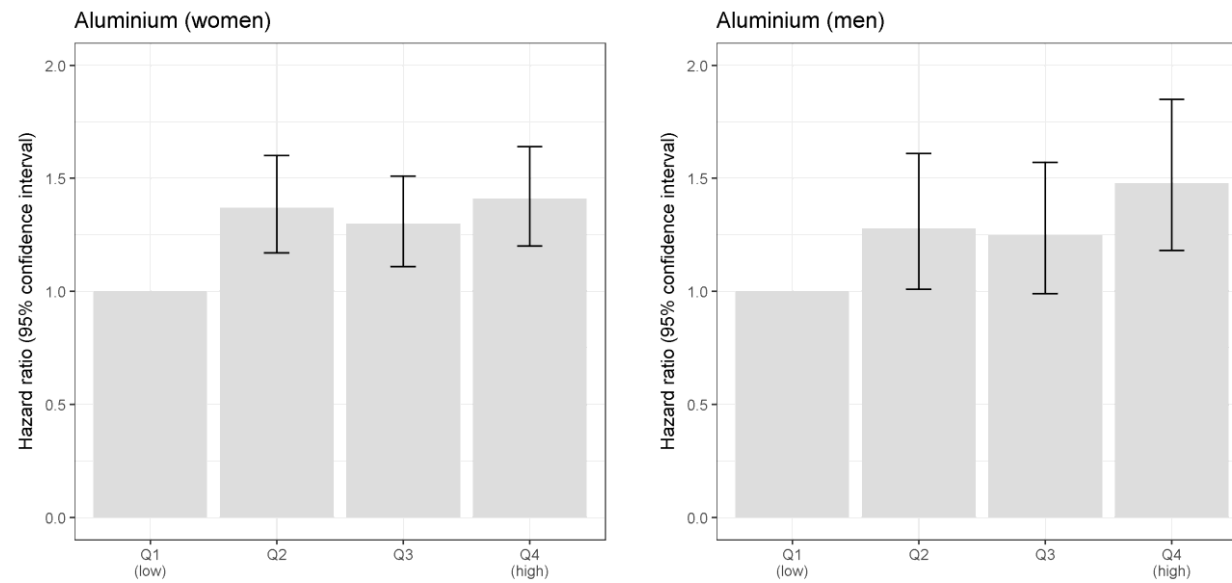
Cut points for fluoride quartiles were 44.4, 48.7, and 56.3µg/L

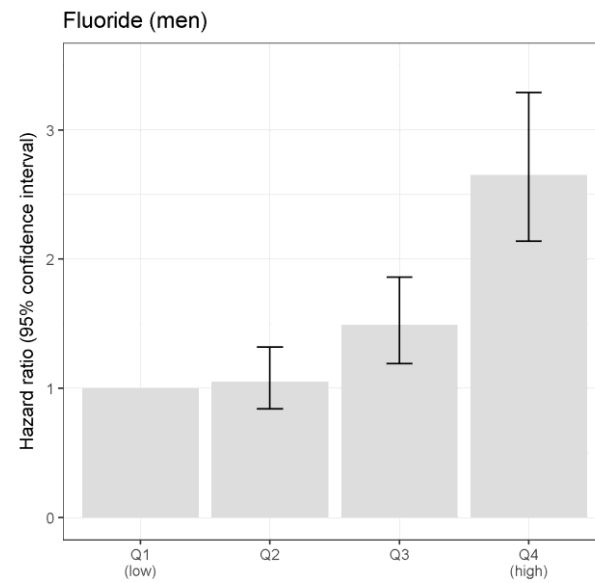
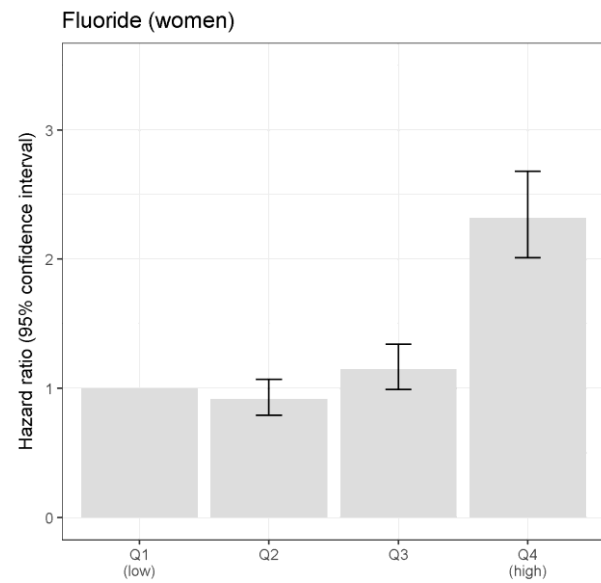
FIGURE 1. Maps indicating mean levels of aluminium (left) and fluoride (right) in drinking water in Scotland 2005-2012: the Scottish Mental Survey 1932 cohort



Lower panel shows an enlarged view of the Central Belt of Scotland including Glasgow and Edinburgh

FIGURE 2. IQ-adjusted hazard ratios and accompanying 95% confidence intervals for the association between mean aluminium and fluoride levels in drinking water and dementia in men and women: the Scottish Mental Survey 1932 cohort





SUPPLEMENTARY TABLE 1. Number of samples and mean concentrations of aluminium and fluoride in drinking water sampling sites in Scotland

2005-2012: the Scottish Mental Survey 1932 cohort

	2005	2006	2007	2008	2009	2010	2011	2012	Overall
Aluminium									
N samples	5285	5367	5356	5273	5232	5197	5062	5096	41868
Mean (sd)	39.2 (44.3)	38.5 (31.7)	38.9 (75.8)	34.0 (29.0)	31.5 (25.5)	31.4 (26.9)	31.3 (28.8)	28.5 (19.6)	34.2 (39.4)
Range	4-1549	2-874	2-5096	4-860	4-878	4-747	4-781	9-222	2-5096
Quartiles	22, 32, 46	22, 32, 47	22, 32, 46	18, 28, 42	81, 26, 39	17, 24, 39	16, 25, 38	16, 23, 35	18, 28, 42
Fluoride									
N samples	1715	1771	1738	1672	1652	1624	1576	1556	13304
Mean (sd)	68.2 (62.7)	44.2 (46.8)	43.6 (35.6)	38.7 (48.6)	36.7 (36.1)	60.0 (37.7)	64.5 (67.2)	80.6 (126.4)	54.2 (65.0)
Range	10-1060	10-1320	10-390	10-1200	10-540	40-610	40-1200	40-2030	10-2030
Quartiles	30, 60, 100	20, 40, 50	20, 30, 50	20, 30, 40	20, 30, 40	40, 50, 70	40, 40, 70	40, 40, 50	30, 40, 60

SUPPLEMENTARY TABLE 2. Adjusted hazard ratios and accompanying 95% confidence intervals for the association between mean aluminium and fluoride levels in drinking water and dementia in men and women: the Scottish Mental Survey 1932 cohort

	N ^a	Dementia N	Hazard ratio ^b (95% confidence interval)				HR ^b (95% CI) per SD increase	P _{trend}
			Q1 (low)	Q2	Q3	Q4 (high)		
Aluminium								
Women: IQ	4262	1350	1 (ref.)	1.37 (1.17, 1.60)	1.30 (1.11, 1.51)	1.41 (1.20, 1.64)	1.09 (1.03, 1.15)	<0.001
Women: IQ and SIMD	4079	1345	1 (ref.)	1.30 (1.11, 1.52)	1.20 (1.03, 1.41)	1.37 (1.17, 1.60)	1.08 (1.03, 1.14)	0.002
Men: IQ	2728	622	1 (ref.)	1.28 (1.01, 1.61)	1.25 (0.99, 1.57)	1.48 (1.18, 1.85)	1.12 (1.03, 1.21)	0.004
Men: IQ and SIMD	2576	619	1 (ref.)	1.22 (0.96, 1.54)	1.17 (0.93, 1.49)	1.42 (1.14, 1.78)	1.10 (1.01, 1.19)	0.014
Fluoride								
Women: IQ	4262	1350	1 (ref.)	0.92 (0.79, 1.07)	1.15 (0.99, 1.34)	2.32 (2.01, 2.68)	1.34 (1.28, 1.41)	<0.001
Women: IQ and SIMD	4079	1345	1 (ref.)	0.88 (0.76, 1.02)	1.11 (0.95, 1.29)	2.18 (1.89, 2.53)	1.32 (1.26, 1.38)	<0.001
Men: IQ	2728	622	1 (ref.)	1.05 (0.84, 1.32)	1.49 (1.19, 1.86)	2.65 (2.14, 3.29)	1.30 (1.22, 1.39)	<0.001
Men: IQ and SIMD	2576	619	1 (ref.)	1.01 (0.80, 1.27)	1.46 (1.16, 1.83)	2.48 (2.00, 3.08)	1.28 (1.20, 1.37)	<0.001

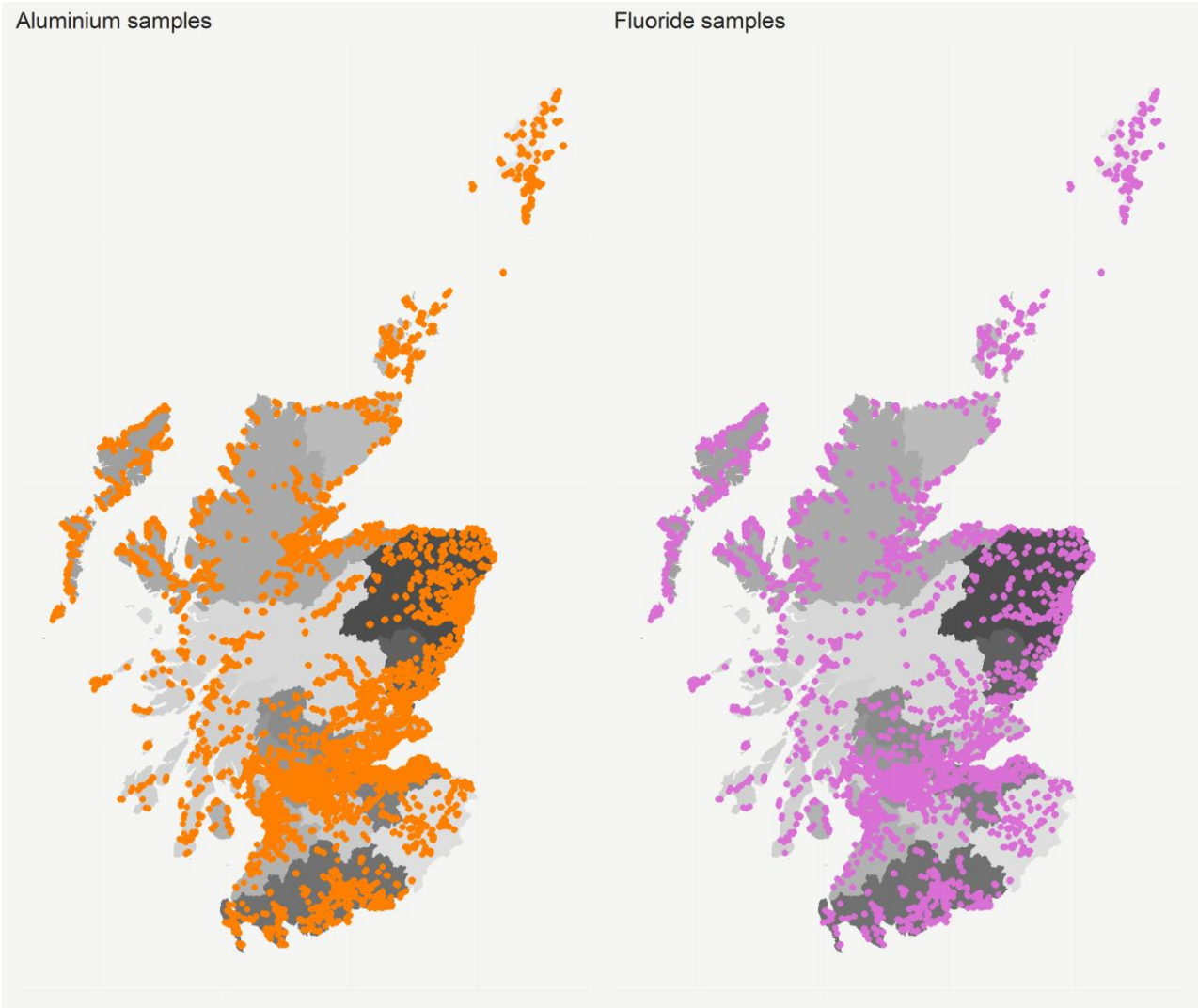
^a SMS1932 participants who survived to 2005 (the start of the exposure period)

^b Hazard ratio adjusted for age 11 mental ability (IQ) or age 11 mental ability and SIMD rank (IQ + SIMD)

Cut points for aluminium quartiles were 30.8, 35.5, and 41.1µg/L

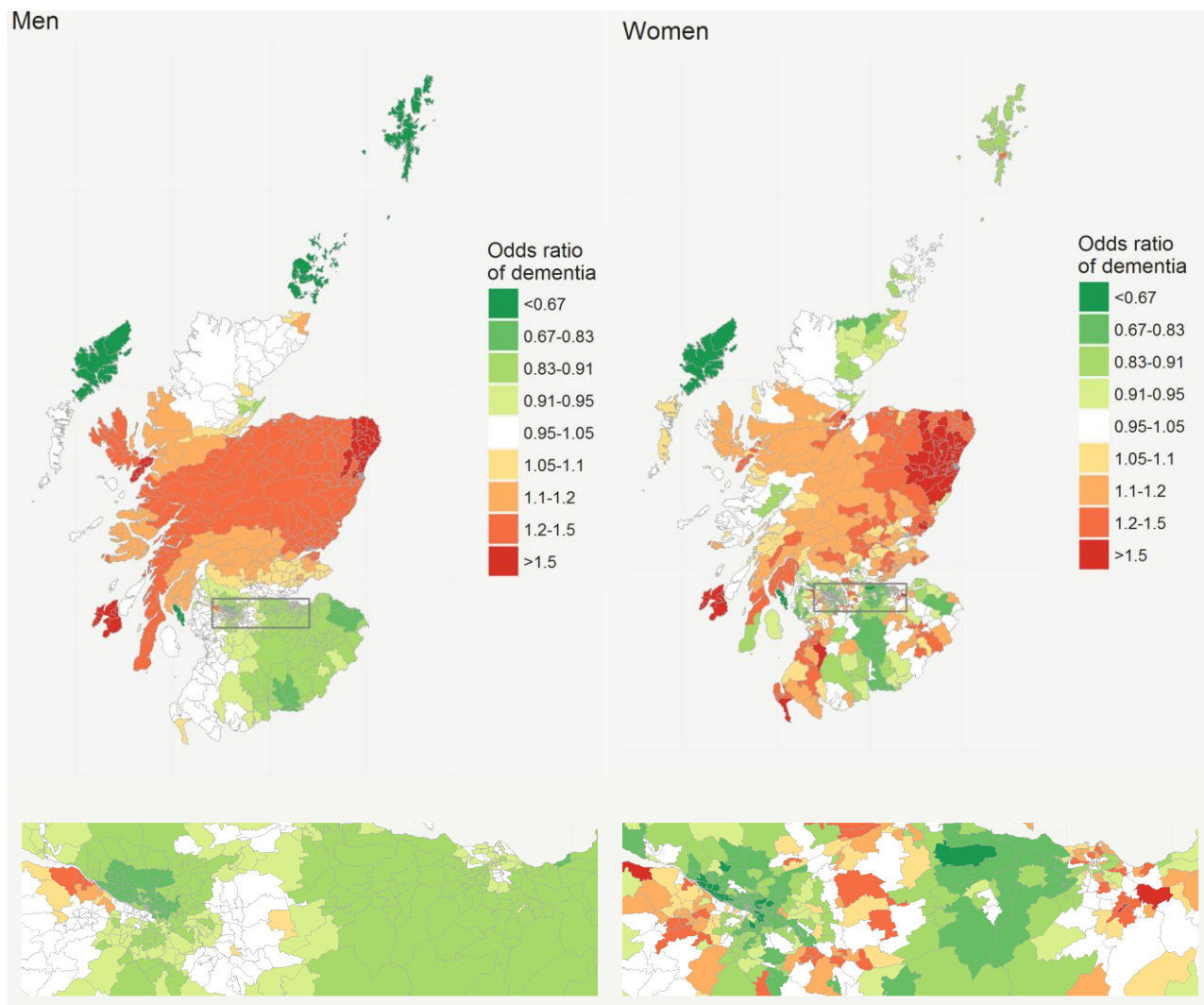
Cut points for fluoride quartiles were 44.4, 48.7, and 56.3µg/L

SUPPLEMENTARY FIGURE 1. Location of aluminium (left) and fluoride (right) sampling sites in Scottish Drinking Water Quality Regulator data 2005-2012: the Scottish Mental Survey 1932 cohort



Postcode areas are shown in different shades of grey

SUPPLEMENTARY FIGURE 2. Odds ratio of dementia in the SMS1932 cohort by adult location with individual-level effects (age) removed: the Scottish Mental Survey 1932 cohort



Lower panel shows an enlarged view of the Central Belt of Scotland including Glasgow and Edinburgh

Adapted from Russ TC, Gatz M, Pedersen NL, Hannah J, Wyper G, Batty GD, et al. Geographical variation in dementia: examining the role of environmental factors in Sweden and Scotland. *Epidemiology* 2015 26(2): 263-70

SUPPLEMENTARY FIGURE 3. Trends in aluminium and fluoride concentrations in drinking water in Scotland from 2005-2012: the Scottish Mental Survey 1932 cohort

